CME Article
Hiv and Hepatitis C Co-Infection

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Infections with hiv and hepatitis c (hcv) are individually severe diseases that call for complex medical managements. Hiv–hcv co-infection complicates the medical management of both diseases. This paper provides an overview of hiv–hcv co-infection with a brief review of the natural history of hepatitis c as it applies to the co-infected patient and recommendations for the diagnosis and medical management of the co-infected patient.

Learning Objectives

i. To review the epidemiology of hiv–hcv co-infection.
ii. To recognize the need to assess hiv infected patients for hcv co-infection.
iii. To describe a treatment regimen for hiv–hcv co-infected patients.

Hepatitis c (hcv) is one of the most frequent infections related to chronic liver disease and currently the most common blood-borne pathogen in the United States. Recent Centers for Disease Control and Prevention (cdc) data estimates 3.9 million Americans have been infected by hepatitis c to date, and approximately 2.7 million of this group have chronic infection with an estimated annual number of chronic liver disease deaths related to hepatitis c ranging from 8,000–10,000. Current cdc disease burden data estimates that 25,000 newly acquired infections have been reported as of 2001, and 4000 acute clinical cases were reported during the same time period. The 1.8% of the general population have at some time been infected with hepatitis c.[1]

The prevalence of hcv co-infection in hiv patients averages 35%, But in hiv clinic populations, where there is a high prevalence of injection drug use (idu) as a risk factor for acquiring hiv, the prevalence may be as high as 80%–90%. High prevalence rates (> 50%) have also been reported in hiv positive inmates at correctional facilities and among patients treated for hemophilia.[2] Currently, 150,000–300,000 persons in the United States are infected with both hiv and hepatitis c. This number represents 15%–30% of all hiv-infected persons by some estimates, and 5%–10% of all hcv-infected persons.[3]

Hepatitis c Disease

Hepatitis c is a single stranded rna virus of the Flaviviridae family. Currently, there are six known genotypes and more than fifty serotypes of this virus. The different genotypes have different worldwide geographic distribution. In the United States, genotype 1 accounts for 75% or more of all hcv infections and is reported to have the poorest response to therapy of all the genotypes.[4]

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HCV is spread predominantly by contact with infected blood or blood products. Prior to 1992, blood transfusion was a leading cause for HCV transmission. Since that time, blood donations are routinely screened for the presence of anti-HCV. Today, the use of shared, unsterilized needles or syringes by injection-drug users; occupational exposure; and, to a lesser extent, maternal–fetal and sexual transmission have been reported as causes of HCV infection.[3,5,6,7] When looking at risk factors for co-infection with HIV, the CDC estimates are that from 50%–90% of HIV-infected drug users are co-infected with HCV.[4] The risk of acquiring HCV through perinatal or sexual exposures is much lower than it would be for HIV and estimates range from 3%–5% risk of transmission.[5] Sporadic transmission, defined as exposure to the virus from cuts, wounds, needle sticks, or procedures occurs in about 10% of acute hepatitis C and in 30% of chronic hepatitis C cases.[6]

Chronic hepatitis C varies greatly in its course and outcome. There are patients who have no signs and symptoms of liver disease. Liver biopsy usually shows some degree of chronic hepatitis, but the degree of liver injury is usually mild, and the overall prognosis may be good. On the other hand, there are patients with severe, symptomatic hepatitis with detectable HCV RNA in serum, and concurrent elevation of hepatic enzymes ultimately evolving to end-stage liver disease, cirrhosis, or hepatic cell carcinoma (HCC).[6] Although approximately 20% of persons who are infected with HCV alone clear HCV RNA from their blood after acute infection, HCV clearance occurs in only 5%–10% of HIV infected persons, less frequently in those with lower CD4+ cell counts.[3] In the co-infected patient, HCV disease progression is enhanced, and end-stage liver disease and cirrhosis may present without significant signs or symptoms heralding its presence.

HIV–HCV Co-infection

It is important to understand how HIV and HCV interact in the co-infected patient. HCV has a direct impact on HIV disease. The phenomenon of co-infection results in more cases of end-stage liver disease and cirrhosis than in HCV alone.[3,7,8,9] HCV CD4+ cell increase may be smaller in the co-infected patient, even with effective anti-HIV therapy. This suggests that HCV may blunt immune recovery. Infection with HIV has been associated with higher HCV RNA viral loads and, in most studies, with more rapid progression of cirrhosis, liver failure, and HCC.[3] Hepatotoxicity caused by antiretroviral drugs is always a concern in a patient with liver disease. The co-infected patient displays greater morbidity and mortality from HCV than from HIV disease alone. Although, highly active antiretroviral therapy (HAART) improves patients' overall HIV indicators, no significant change occurs in alanine aminotransferase (ALT) and HCV RNA levels.[10] In the era of HAART, clinicians now must concern themselves with addressing the co-morbidities of patients living with HIV–AIDS and HCV.

DIAGNOSIS

The diagnosis of hepatitis C should be entertained in all HIV positive patients. In order to formulate a care plan, a complete hepatitis profile is advisable for all HIV positive patients. Liver enzyme abnormalities alone are not an accurate predictor of infection with hepatitis C and should not be relied upon as a screening test for HCV or other types of hepatitis. Initially, screening for HCV should include an HCV Enzyme Immunoassay (EIA). If the HCV EIA is negative in a patient at risk for HCV, a PCR for HCV RNA should be considered. A patient with a positive HCV EIA should have an HCV RNA PCR to confirm the presence of viremia.[2] If viremia is evident, an HCV genotype is warranted. This will provide useful information in planning future treatment options. Because there are no clinical, biochemical, or virologic factors that could reliably identify patients with advanced fibrosis or cirrhosis,[7] a liver biopsy in all co-infected patients is needed. In addition, if treatment of HCV is being considered, thyroid stimulating hormone (TSH), complete blood count (CBC), prothrombin time (PT), ferritin, alpha-fetoprotein (AFP), anti-nuclear antibody (ANA), and liver function studies (LFTs) should be part of the

initial evaluation.[2] A psychiatric evaluation should be performed because of the increased incidence of neuropsychiatric events observed in patients with chronic diseases and in those patients being treated with interferon (IFN) for HCV.

TREATMENT

In 2002 the NIH consensus statement recommended that, although there were no specific HCV therapies approved for the co-infected patient, these patients should be considered for treatment.[4] Currently, there are no therapies that have been approved by the Food and Drug Administration (FDA) for the treatment of the HIV–HCV co-infected patient, although preliminary studies suggest the combination of Pegylated Alpha Interferon (PEG-Intron A)/ Ribavirin (Rebtrol) is an optimal therapy in the co-infected patient.[3,6] The recommended dose of IFN and Ribavirin are based on body weight. In combination therapy, the recommended does of PEG-Intron are 1.5 micrograms per kilogram per week, in a single weekly dose. The recommended Rebetrol dose is 600–800 mg twice a day. Dose reductions are recommended in patients with renal failure.[11]

PEG-Intron is contraindicated in those patients with autoimmune hepatitis or decompensated liver disease. Additionally, combination therapy is contraindicated in patients with hemoglobinopathies, in women who are pregnant, and in men whose female partner is pregnant. If a man with hepatitis C is being treated and his female partner is pregnant, teratrogenic effects to the fetus can be observered secondary to the teratogenic effects of ribavirin.[11]

The patient should be closely monitored during therapy for adverse reactions, some of which may be life threatening. They include suicidal–homicidal ideation, depression–anxiety, psychosis, and relapsing substance abuse issues, which underscores the importance of a psychiatric evaluation prior to initiation of therapy. The treatment may aggravate thyroid disorders and precipitate hyperglycemia. Pancreatitis and bone marrow suppression has been observed. Hypotension, cardiac arrhythmia, and myocardial infarction with IFN have been reported. Pulmonary disorders including pneumonia, dyspnea, and interstitial pneumonitis may be induced or aggravated with therapy. Abdominal pain and fatal ulcerative–ischemic colitis may be seen within the first three months of therapy. Exacerbation or development of autoimmune disorders may occur, and various ophthalmologic conditions have been reported. Rarely, hypersensitivity reactions have occurred. Constitutional symptoms of myalgia, headache, nausea, vomiting, fatigue, and other flu-like symptoms are expected findings at the initiation of therapy, but should subside within a few weeks.

Concomitant use of benzodiazepines may result in hepatoxicity. Methadone has been found to be less effective in those who are receiving IFN therapy. Various nucleoside reverse transcriptase analogues (NRTI) have been found to interact with IFN, although to date, clinically significant antagonism has not been documented.[3,11]

The initiation of HAART may be limited by either HCV-related liver disease or the hepatotoxicity of the medications in concert with viral liver disease.[12] Overall, researchers have found that there were proportionately more deaths in the HIV–HCV cohort group when compared to a control group of HIV mono-infected patients' survival;[8] however, the co-infected patient receiving HAART had similar durations of survival when compared to the HIV mono-infected patient. This implies that managing HIV disease plays a major role in overall survival in the co-infected patient and that managing the potential hepatotoxicities of these medications continues to be a major challenge to clinicians.

Histological improvement on repeat liver biopsy was frequently observed in patients receiving interferon therapy, even without the absence of HCV clearance.[13] A small cohort study in Japan also found that in the co-infected patient, the use of high doses of interferon reduced viral burden of both HIV and HCV.[14] An important finding of the AIDS Clinical Trial Group (ACTG) protocol A5071, is that, while there were more toxicities associated with the use of PEG-Intron, no negative impact was seen on

parameters used for monitoring HIV disease.[15] There are on-going studies to evaluate the safety, efficacy, and pharmacokinetics of combination HCV therapy in conjunction with HAART, but caution should be exercised when using simultaneous treatments. Treatment of HCV and HIV should not be initiated simultaneously.

To date there is no solid consensus to the answer of the question, "Which disease should be treated first, HIV or HCV?" Surely this is a fertile area for future research. Certainly it has become evident that the progression of HCV in the co-infected patient is more rapid than in the mono-infected HCV patient, and mortality is improved with initiation and use of HAART in the co-infected patient.[8] It is of the utmost importance that in a co-infected patient, both disease entities be serologically and histologically pursued before any treatment regimen is contemplated. The potential toxicities and interactions of the medications used must be anticipated and minimized to assure the most optimal outcome, and patients must be educated accordingly. If there is relative stability in a patient's HIV disease, (CD4+ $\geq$ 350, HIV RNA $\leq$ 55,000), it may be more prudent to treat HCV first; however, if this is not the case, considering the initiation of HAART is warranted.

LABORATORY WORK

As with all patients, close and frequent follow-up is a necessity. Initially, a complete blood count and LFTs should be evaluated every 2 weeks for the first month of therapy, and then every 1–2 months thereafter. Dose adjustments of IFN and of Ribavirin may need to be made at that time. HIV RNA and CD4+ cell count should be performed at week 12 of therapy, and an HCV RNA PCR should be measured at week 24. If there is undetectable HCV RNA, therapy is continued for an additional 24 weeks. Some clinicians will stop therapy at this time in persons with HCV genotype 2 or 3; this approach has not been evaluated in the co-infected patient.[3] Periodic evaluation of electrolytes and of kidney function is warranted. At the end of therapy and six months thereafter an HCV RNA PCR should be completed. If the HCV RNA is undetectable 6 months after stopping therapy, the chance of virologic relapse is low.[3] Data on sustained virologic response (SVR) is not available; however, approximately 23% of co-infected patients had undetectable HCV RNA after 12 weeks of combination therapy.[3] Few options exist for patients who either do not respond to therapy, or who respond, and later relapse. The use of long-term therapy/continual therapy for those patients who initially responded to therapy may be an option; however, this requires further investigation.[4]

ADDITIONAL CONSIDERATIONS

In addition to the use of antiviral agents, a patient's immunization status should be assessed. Immunizations for hepatitis A (HAV) and hepatitis B (HBV) should be given in all patients when appropriate. The pneumoccocal and yearly influenza vaccine is appropriate for all patients. Counseling related to the use of dietary supplements, especially vitamin A or iron should be addressed, as these substances accumulate in the liver. Abstinence from alcohol intake or other substance abuse must be stressed.

Summary

Understanding of the co-infected patient continues to evolve. Currently the majority of research, diagnosis, and treatment options have been geared to the mono-infected HIV or HCV patient. The dynamics created by the interactions of these two disease entities requires the clinician to understand the complexity of evaluating, diagnosing, and treating the co-infected patient. Future research should be designed to evaluate novel, safe, and efficacious therapies to optimize the outcome in this growing population. *NJM*

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1. What is the prevalence of HIV–HCV co-infection among HIV infected injection drug users?
   A. 60%–70%
   B. 70%–80%
   C. 80%–90%
   D. 90%–100%

2. Which of the best describes the impact of HCV on HIV disease?
   A. Blunt CD4+ cell recovery
   B. Decreases HIV viral load
   C. Decreases HIV disease progression
   D. No influence

3. What initial test should be performed in HIV infected patients to assess their HCV status?
   A. HCV EIA
   B. HCV RNA
   C. Liver biopsy
   D. Liver function studies

4. Which of the following is a contraindication for pegylated interferon?
   A. Hepatitis B infection
   B. Hiv infection
   C. Pregnancy
   D. Renal disease

5. At what point during therapy should HCV RNA be re-evaluated?
   A. 12 weeks
   B. 24 weeks
   C. 36 weeks
   D. 48 weeks

Answer Sheet

"Hiv and Hepatitis C Co-infection"

Darken the correct answers

1. [A] [B] [C] [D]
2. [A] [B] [C] [D]
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